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ANTIDIABETIC ACTIVITY OF SULFONYLUREAS- A REVIEW

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Abstract:
Diabetes Mellitus is a chronic disease represented with high glucose blood levels. Although sulfonylurea compounds are the second preferred drug to treat Type II Diabetes (TYIID), they are still the most used agents due to their lower cost and as a mono-dosing. They are often prescribed for diabetic patients who are not of overweight or those for whom metformin is contraindicated or is not enough to achieve adequate glycemia control. They function by increasing insulin secretion from pancreatic beta cells. In the present study we will review various class of sulfonyl ureas.

Key words*- sulfonylureas, chemistry, Structural activity relationship*

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INTRODUCTION:

Sulfonyl ureas are commonly used in type II diabetes treatment. They are often prescribed for diabetic patients who are not of overweight or those for whom metformin is contraindicated or is not enough to achieve adequate glycemia control. Their hypoglycemic activity was first noticed by Ruiz in 1937 when he was doing experiments on sulfa drugs. Later on, in 1942, Jabon confirmed this efficacy when anti-bacterial sulfonamide; p-amino sulfonamide isopropyl thiodiazole, caused hypoglycemic activity as side effect while treating patients for typhoid. Studies on sulfonamide bioactivities expanded as Laboratories proved that sulfa drugs stimulated β-cell release of insulin. In 1950s, Carbutamide; 1-butyl-3 sulfonylurea, was the first sulfonylurea compound presented in the clinical use for diabetes therapy, yet not for too long as it had adverse effects on bone marrow[1]. In 1956, Germany introduced tolbutamide; sulfa drugs derivate, as the first sulfonylurea compound to be in clinical use of diabetes treatment. Other first generation sulfonylurea compounds such as acetohexamide, tolazamide, and chlorpropamide were available in the German market. Glyburide and glipizide; more potent sulfonylurea members entered the US drug market in 1984; more than a decade of their usage in Europe. Furthermore, Glimepiride, the most potent sulfonylurea compound, was not commercially introduced till 1995 in the US drug market[2].

Classification

First generation

- Acetohexamide – used mainly for people whose diabetes cannot be controlled by diet alone.
- Chlorpropamide – a long-acting sulphonylurea. It has more side effects than other sulphonylureas and its use is no longer recommended.
- Tolbutamide – generally has a short duration of action due to its rapid metabolism, and is therefore safe for use in elderly diabetics.
- Tolazamide – other diabetes medicines are sometimes used in combination with tolazamide if needed.

Second generation

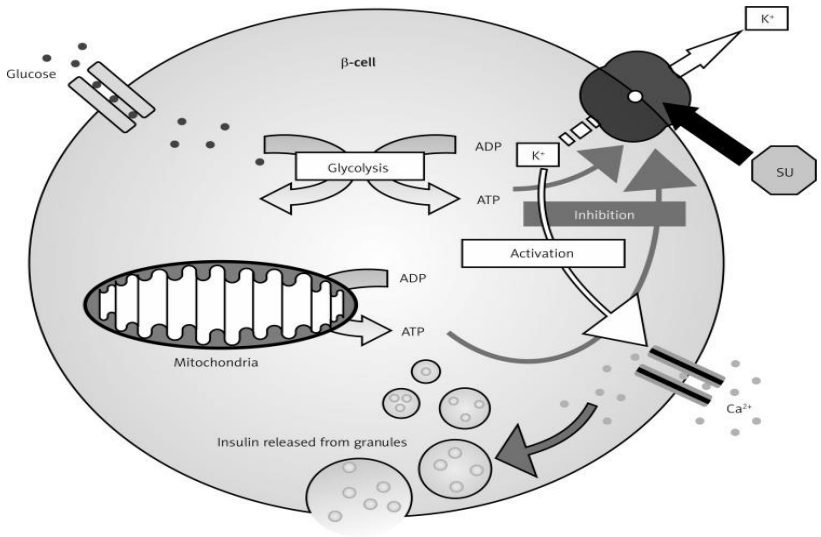
- Glipizide – is an oral medium-to-long acting anti-diabetic drug.
- Gliclazide – classification has been ambiguous, as literature uses it as both a first-generation and second-generation sulfonylurea.
- Glibenclamide (glyburide) – a major cause of drug induced hypoglycemia. Cholestatic jaundice is noted.
- Gliquidone – in addition to its primary function, it assists on the movement of sugar in the blood into the cells in the body.

Third generation

- Glimepiride – also is available in combination with other diabetes medications such as Rosiglitazone[3,4]

Mechanism of action

The main effect of sulfonylureas is the rise in plasma insulin concentrations; consequently, they are effective only when residual pancreatic β-cells are present. The rise in plasma insulin levels occurs for two reasons. Firstly, there is stimulation of insulin secretion by pancreatic β-cells, and secondly, there is a decrease in hepatic clearance of insulin. In particular, this second effect appears mainly after the increase of insulin secretion has taken place. In fact, in the first month of treatment, the levels of insulin and insulin response to glucose rise rapidly, resulting in lowered blood glucose. After this period, baseline and stimulated insulin levels become lower compared to those measured at the beginning of treatment; however, blood glucose values remain unchanged. The reason for this observation is not clear. With regard to the secretory activity of sulfonylureas, the mechanism is now known. They act by binding to the specific receptor for sulfonylureas on β-pancreatic cells, blocking the inflow of potassium (K^+) through the ATP-dependent channel: the flow of K^+ within the β-cell goes to zero, the cell membrane becomes depolarized, thus removing the electric screen which prevents the diffusion of calcium into the cytosol[5,6]. The increased flow of calcium into β-cells causes the contraction of the filaments of actomyosin responsible for the exocytosis of insulin, which is therefore promptly secreted in large amounts



Mechanism of action of sulfonylureas

On the top right corner is represented the SUR, while octagon is sulfonylurea (SU). When the SU binds SUR, the flow of K (arrows) stopped, so the cell membrane is depolarized. An increased flow of calcium cause the contraction of the filaments of actomyosin responsible for the exocytosis of insulin

In particular, the sulfonylureas receptor (SUR1), a 1581-amino acid protein, has high affinity for glibenclamide. SUR1 is a member of the ATP-binding cassette (ABC) super-family that has two nucleotide binding folds (NBF-1 and NBF-2). Each nucleotide binding fold contains the Walker A and B motifs and the SGGQ ABC signature, and it is important in nucleotide regulation of the functional activities of ABC proteins. SUR1 has three transmembrane domains (TMD), TMD0, TMD1 and TMD2, which consist respectively of 5, 6 and 6 transmembrane (TM) segments that are numerated progressively. TMD0 contains the TM segments from 1 to 5, TMD1 contains the TM segments from 6 to 11, and TMD2 contains the TM segments from 12 to 17. SUR1 is expressed at higher levels in pancreatic islets. SUR1 is also present in the brain. Also a second type of sulfonylureas receptor exists; it is named SUR2A (formerly called SUR2), and it is an isoform of SUR1. SUR2A is a protein of 1545 amino acids sharing 68% amino acid identity with SUR1. SUR2A has a low affinity for glibenclamide. Several variants of SUR2A have also been identified. One of them, SUR2B, differs from SUR2A by 42 amino acids in the C-terminus, where it is, instead, similar to SUR1. Although SUR2A is expressed predominantly in heart and skeletal muscle, SUR2B is expressed widely in other tissues. In the past a two-site model (A site and B site) had been proposed for the interaction between sulfonylureas, glinides and SUR. The A site is located on the eighth (between TM segments 15 and 16) cytosolic loop, which is specific for SUR1. Instead the B site involves the third (between TM segments 5 and 6) cytosolic loop, which is very similar in all SURs. According to these different sites of interaction, sulfonylureas and glinides can be divided into three groups. The first of these includes nateglinide, tolbutamide and gliclazide, which are molecules that bind specifically the A site of SUR1, while the second group, which includes glimepiride and glibenclamide, binds non-specifically the B sites of both SUR1 and SUR2A as well as the A site of SUR1; finally, the third group (which includes meglitinide and repaglinide) binds to the B site of SUR1 and SUR2A[7,8].

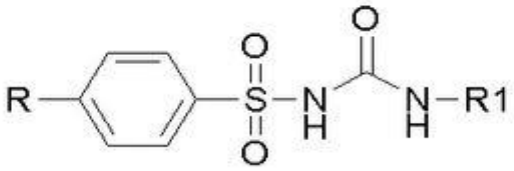
Beside the “first phase”, sulfonylureas also increase the “second phase” of insulin secretion that begins 10 min later as insulin granules are translocated to the membrane of the β-cell. This second phase involves the progressive formation of new insulin granules, and it is possible only if β-cell function is preserved. It is important to underline that the release of insulin induced by sulfonylureas is independent of glucose levels, and this can increase the risk of hypoglycemia.

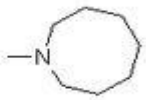
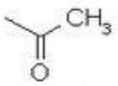
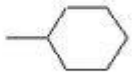
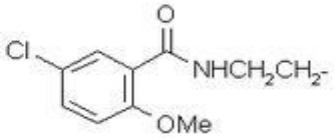
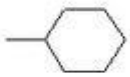
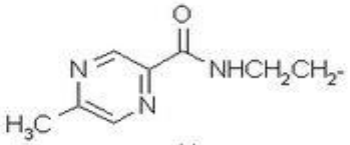
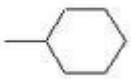
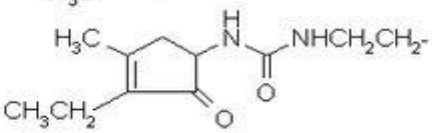
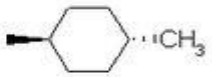
The impairment of the effect on insulin secretion that occurs during chronic administration of sulfonylureas is due to the down-regulation of the receptor for sulfonylureas on the surface of β-cells. This phenomenon disappears after discontinuing treatment for a period of time. In fact, resuming the administration of these drugs, the first administration effect reappears. Through a similar mechanism sulfonylureas can stimulate the secretion of somatostatin and suppress the secretion of glucagon in δ-cells and α-cells. In addition to the β-cells of the pancreas, sulfonylureas exert their effects on other cells. As an example, an increase of receptors for insulin present on monocytes, adipocytes and erythrocytes has been demonstrated in patients chronically treated with sulfonylureas. Moreover, sulfonylureas seem to exert other effects

as well: they increase peripheral glucose utilization by two mechanisms of action, by stimulating hepatic gluconeogenesis, and by increasing the number and sensitivity of insulin receptors. However, their main effect is an increased responsiveness of β-cells to both glucose and non-glucose secretagogues (such as amino acids), resulting in more insulin released at any blood glucose concentration. Moreover, and this fact should not be underrated, they may cause suppression, sometimes significant, of overnight hepatic glucose output, thus further lowering the fasting blood glucose concentration[9,10,11].

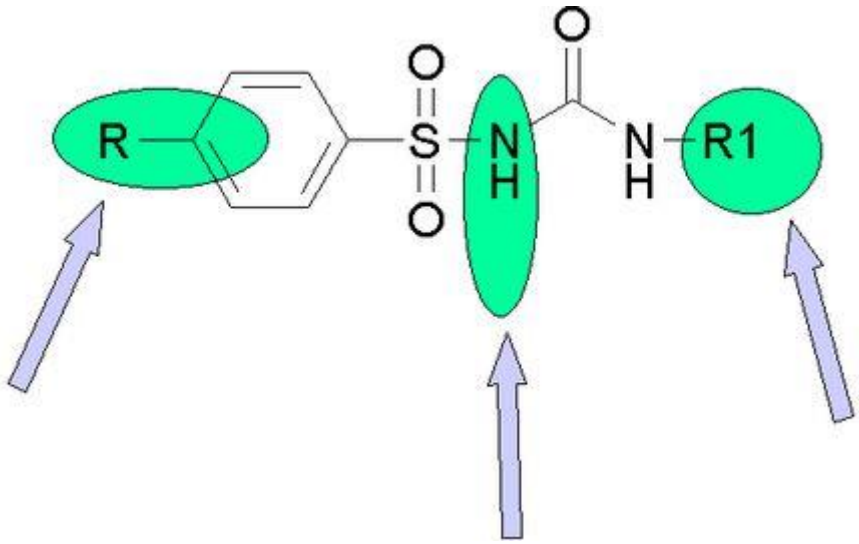
Chemistry and Structural activity relationship

Tolbutamide, Chlorpropamide, Tolazamide and Acetohexamide are first generation sulfonylureas while Glyburide and Glipizide are second generation.



name	R	R1
Tolbutamide	$-CH_3$	$-CH_2CH_2CH_2CH_3$
Chlorpropamide	$-Cl$	$-CH_2CH_2CH_3$
Tolazamide	$-CH_3$	
Acetohaxamide		
Glyburide		
Glipizide		
Glimepiride		

- The benzene ring should contain one substituent, preferably in the para position. The substituents that seem to enhance hypoglycemic activity are methyl, amino, acetyl, chloro, bromo, methylthio, and trifluoromethyl groups.
- Compounds with p-(-b-arylcarboxamidoethyl) substituents (the second generation agents) are orders of magnitude better than the first generation agents. It is believed that this is because of a specific distance between the nitrogen atom of the substituent and the sulfonamide nitrogen atom.
- The group attached to the terminal nitrogen should be of certain size and should impart lipophilic properties to the molecule. The N-methyl are inactive, N-ethyl have low activity, while N-propyl to N-hexyl are most active. Activity is lost if N-substituent contains 12 or more carbons[12,13,14].



Structural activity relationship

Metabolism and Pharmacokinetics

The sulfonyl ureas are rapidly absorbed from the GI tract. This is understandable taking into consideration their highly hydrophobic nature. Due to this nature they are highly protein bound. Second generation sulfonyl ureas due to their greater hydrophobic character are effective over a longer duration of action.

Chlorpropamide is active over an extended period of time because chlorine atom suppresses the rate of metabolism. Despite report to the contrary chlorpropamide does undergo significant metabolism, only slowly. The primary metabolites are 2-hydroxy and 3-hydroxy chlorpropamide[15,16,17].

Hydroxylation of the aromatic ring appears to be the most favored metabolic pathway for these sulfonyl ureas. The hydroxylated derivatives have much lower hypoglycemic activity than the parent compounds.

The alkyl group of the sulfonyl urea also undergoes hydroxylation. For example, Glipizide is metabolized to cis-3-hydroxy-glipizide and trans-4-hydroxy-glipizide. These metabolites have ~15% of the hypoglycemic activity of the parent compound[18,19,20].

Agent	Equivalent therapeutic dose (mg)	Serum protein binding (%)	Half-life (h)	Duration of action (h)	Mode of metabolism
Tolbutamide	1000	95 - 97	4.5-6.5	6-12	carboxylation
Chlorpropamide	250	88 - 96	36	~60	cleavage, hydroxylation
Tolazamide	250	94	7	12-14	carboxylation, hydroxylation
Acetohexamide	500	65 - 88	6-8	12 - 18	reduction, hydroxylation
Glyburide	5	99	1.5-3.0	~24	hydroxylation
Glipizide	5	92 - 97	4	~24	hydroxylation

Side effects

sulfonylureas are usually well tolerated. the most common side effect is hypoglycemia, more common with long-acting sulfonylureas such as chlorpropamide and glibenclamide[23,24,25]. however, all sulfonylureas may cause hypoglycemia, usually due to an excessive dosage. it is important to remember that hypoglycemia may persist for many hours and require in-hospital treatment.

A 4-year retrospective study of 14,000 patients, 65 years or older, with type 2 diabetes, treated with different sulfonylurea drugs, showed that episodes of serious hypoglycemia were rare[26]. the incidence was higher in those patients taking glibenclamide, and lower among those taking tolbutamide (19.9 vs. 3.5 episodes per 1000 person-years, respectively). other shorter-acting drugs, such as tolazamide and glipizide, were also associated with a lower incidence, while the incidence with chlorpropamide was similar to that with glibenclamide. patients recently discharged from

hospital were at the highest risk (4.5 episodes per 100 person-years)[26].

patients should be cautioned about those situations in which hypoglycemia is most likely to occur: after exercise or a missed meal, or when taking an excessive dosage. in addition to the use of longer-acting drugs such as glibenclamide or chlorpropamide, it is necessary to recognize other situations at risk of hypoglycemia. for example, sulfonylureas should be used with caution in patients who are undernourished or alcohol abusers, in patients with impaired renal or cardiac function or gastrointestinal disease, in patients concurrently treated with salicylates, sulfonamides, fibric acid derivatives (such as gemfibrozil), and warfarin[27], and during hospitalization[28].

a good way to prevent hypoglycemia is to start therapy with sulfonylureas at a low dose. the dosage may be increased at intervals of 2–4 weeks until the glycemic target is reached. obviously, self-monitoring of blood glucose by the patient may be helpful. nevertheless, in general, patients who have managed less fasting hyperglycemia after a trial of diet and exercise are more likely to develop hypoglycemia.

the reported frequency of sulfonylurea-related hypoglycemia in the elderly is variable, and frequently underestimated (usually only severe hypoglycemias are considered). even though this risk is lower with the newer sulfonylureas (glipizide, glimepiride)[24], these episodes, more frequent and dangerous in the elderly, can limit their use. in fact, in these patients, autonomic failure, secondary to aging and to longer duration of diabetes, is responsible for asymptomatic and occult hypoglycemias, while difficulty in communication may complicate its management. the concept of the "frail elderly", in which the glycated haemoglobin (hba_{1c}) target was raised up to 8.6%, allows less aggressive therapeutic strategies to be followed, and does not justify the use of drugs that carry a risk of prolonged hypoglycemia. thus, old age (> 75 years), renal impairment and liver disease are conditions in which sulfonylureas should not be used as first line therapy, but as second or third line agents in type 2 diabetes mellitus.

sulfonylureas act directly on β-cells, leading to progressive dysfunction and worsening of insulin secretion. thus, despite better glycemic control in the short term, diabetes could worsen in the long term. the clinical result of this phenomenon is known as "secondary failure", and it represents the inevitable fate of all oral hypoglycemic agents, especially older sulfonylureas. in fact, patients with previous higher dosages and longer treatment with sulfonylureas display a worse response to insulin after changing therapy: sulfonylurea dosage is independently associated with inadequate response to insulin analogues in patients with secondary failure[29].

weight gain is an almost constant counterpart of treatment with sulfonylureas, even though to a lesser degree than that recorded with insulin[30]. this certainly constitutes a deleterious effect, especially in reference to a chronic illness such as diabetes mellitus, where the control of body weight represents, perhaps, the main target of treatment. fortunately, the weight gain is usually mitigated by the concurrent administration of metformin.

other infrequent side effects that may occur with all sulfonylureas include nausea, skin reactions such as erythema multiforme, exfoliative dermatitis and also, more rarely, photosensitivity. occasionally, they can cause abnormalities in liver function tests, which may rarely lead to cholestatic jaundice, hepatitis and hepatic failure. it seems especially important to recall some disturbing side effects of chlorpropamide, fortunately no longer used, mainly because of its very prolonged duration of action. it may cause, in fact, a flushing skin reaction after alcohol ingestion by inhibiting the metabolism of acetaldehyde[31]; it also may lead to hyponatremia by increasing the secretion of anti-diuretic hormone[32]. this effect has also been described with the use of glimepiride and glipizide.

some studies suggest that sulfonylureas may affect cardiac function and also may be associated with poorer outcomes after myocardial infarction[33,34,35]. an increased mortality from cardiovascular disease in diabetic patients taking tolbutamide was reported in the past decades (university group diabetes study) [36].

subsequently, several studies were designed to shed light on this alarming association. in the mayo clinic, in 185 consecutive diabetic patients undergoing percutaneous coronary intervention after myocardial infarction, the odds ratio for death was 2.77 for patients treated with a sulfonylurea at the time of the myocardial infarction[37].

in the digami (diabetes mellitus, insulin glucose infusion in acute myocardial infarction) trial, the patients treated with a sulfonylurea at the time of myocardial infarction were those with the poorest outcome [38].

finally, in a retrospective canadian study using pharmaceutical data for 5795 subjects who received initial monotherapy with either a sulfonylurea or

metformin, deaths per 1000 person-years during the follow-up period (mean 4.8 years) were 67.6 for first-generation sulfonylurea medications, 61.4 for glibenclamide, and 39.6 for metformin[39]. the risk of death or of an acute ischemic event was greater for subjects exposed to higher amounts of the sulfonylurea, but not to metformin[39]. the greatest risk was for subjects treated with tolbutamide or chlorpropamide (hazard ratio (hr) 2.1, 95% ci: 1.0–4.7). an explanation of these results may be found in the interaction of sulfonylureas with cardiomyocytes. indeed, there are sulfonylurea receptor isoforms on cardiac myocytes and vascular smooth muscle. insulin secretagogues display different tissue selectivity characteristics at therapeutic concentrations, and this may translate into different levels of cardiovascular risk[40]. since atp-dependent k^+ channels are present on cardiac cells and coronary vessels, sulfonylureas, if present at the time of a myocardial infarction, may impair adequate coronary vasodilatation, thus resulting in a larger area of myocardial damage. other hypotheses for the effect of sulfonylurea medications on cardiovascular events and mortality are founded on interference with ischemic preconditioning, or possible arrhythmogenic effects, and on the inhibitory effect of sulfonylureas on the reverse cholesterol transport mediated by hdl [41]. the treatment with sulfonylureas also carries other implications. in fact, there is evidence suggesting that the activation of mitochondrial k^+ atp channels plays an important role in the mechanical protection that results from ischemic preconditioning [41]. glibenclamide prevents cardioprotection induced by ischemia with the interaction with mitochondrial k^+ atp channels, whereas gliclazide does not. in skeletal muscle, activation of k^+ atp channels during fatigue prevents muscle dysfunction by reducing resting tension and improving force recovery. however, blocking k^+ atp channels of skeletal muscles by glibenclamide does not affect the fall in force during fatigue. k^+ atp channels can mediate counter-regulatory responses to hypoglycemia, at the level of the central nervous system[42]. the opening of k^+ atp channels during hypoxia also reduces membrane excitability and protects neurons from seizure activity. it has to be underlined that newer sulfonylureas, such as gliclazide, are selective for the pancreatic sulfonylurea receptors over the cardiac receptors and do not appear to be associated with increased cardiovascular mortality compared with metformin or other anti-diabetic medications [43], although direct controlled clinical trials have not been performed[44,45]. in a study of 1310 french patients with diabetes who were hospitalized for myocardial infarction, in-hospital mortality rates were significantly lower in patients previously treated with sulfonylureas compared with other oral medications, insulin, or no medication (3.9%, 6.4%, 9.4%, and 8.4%, respectively, odds ratio for patients receiving sulfonylureas before admission compared with no sulfonylureas 0.50, 95% ci: 0.27–0.94)[44]. among the sulfonylurea-treated patients, mortality was significantly lower in patients receiving gliclazide or glimepiride rather than glibenclamide, which is not selective for the pancreatic sulfonylurea receptors.

In addition to these findings, the results of clinical trials, particularly advance, using newer sulfonylureas such as gliclazide, are somewhat reassuring, although they were not specifically designed to address this issue. moreover, it has been demonstrated that the use of sulfonylureas can increase the risk of developing a neoplastic disease regarding the relation between sulfonylurea use and cancer, the evidence is weak: bowker *et al*. found that cancer-related mortality among residents of the province of saskatchewan in canada was greater for diabetics treated with insulin and sulfonylureas than for metformin users. however, from this study the relationship between sulfonylurea use and cancer development was inconsistent. in fact, many factors must be considered when analyzing the findings from observational studies that examine the association between diabetes therapies and cancer, for example sample size of the population examined, type and duration of diabetes, the level of metabolic control, comorbidities, and duration of follow-up. we know that sulfonylureas are a heterogeneous group of drugs, and the effects of single drugs are drug-specific rather than class-specific. looking at the study performed by monami *et al*., it seems that cancer and its related mortality in patients with type 2 diabetes mellitus using glibenclamide was significantly higher than in those using gliclazide. furthermore, regarding colorectal cancer, there is no evidence that using sulfonylureas in type 2 diabetes leads to cancer: rather, the risk of developing colorectal cancer in these patients is reduced.

CONCLUSIONS:

Despite the great number of anti-diabetic agents currently available in clinical practice, sulfonylureas are still frequently used: maybe this is due to their lower cost, to the possibility of mono-dosing and to the presence of an association with metformin in the same tablet.

In patients suffering from inadequate glycemic control, sulfonylureas can rapidly achieve significant improvement when added to metformin . According to recent guidelines, they can also be associated with glitazones , GPL-1 analogues, DPP-4 inhibitors or long acting insulin when the association with metformin alone fails to achieve the glycemic target. Considering adverse events,

sulfonylureas, especially the older ones, are linked to a greater prevalence of hypoglycemia, and cardiovascular risk; in this respect, newer prolonged-release preparations of sulfonylureas are undoubtedly safer, mainly due to reducing hypoglycemia, and for this reason should be preferred.

We can conclude that sulfonylureas should be used in relatively young patients for a limited period of time, maybe 3–6 months, in order to rapidly achieve adequate glycemic control. In this way we can avoid starting insulin, improving the patient's quality of life and his/her compliance and reducing the cost of anti-diabetic therapy. After 3–6 months, if adequate glycemic control has not been achieved, we should start insulin treatment. On the other hand, if we have reached a lower HbA_{1c}, we should replace sulfonylureas with other oral anti-diabetic agents, according to the guidelines.

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